Cognitive therapy for people with schizophrenia spectrum disorders not taking antipsychotic medication

Cognitive therapy for people with schizophrenia spectrum disorders not taking antipsychotic medication: A randomised controlled trial

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Abstract

Objective: To determine whether cognitive therapy (CT) is effective in reducing psychiatric symptoms experienced by people with schizophrenia spectrum disorders that have chosen not to take antipsychotic medication.

Design: A two-site single-blind randomised controlled trial comparing CT plus treatment as usual (TAU) with TAU only. Participants were followed-up for a minimum of 9 and a maximum of 18 months.

Setting: Diverse services at two UK sites

Participants: 74 participants with schizophrenia spectrum disorders who had chosen not to take antipsychotic medication psychosis (aged 16-65 years; mean 31.47; SD 12.27) were recruited. 37 were assigned to CT and 37 to TAU.

Intervention: CT incorporated up to 26 sessions over 9 months (mean sessions = 13.30) plus up to four booster sessions.

Main outcome measures: Primary outcome was the Positive and Negative Syndrome Scale (PANSS) total score, which provides a continuous measure of psychiatric symptoms associated with schizophrenia spectrum disorders on the basis of a commonly used structured psychiatric interview.

Results: Changes in outcomes were analysed following the intention-to-treat principle, using random effects regression (a repeated-measures ANCOVA) adjusted for site, age, gender and baseline symptoms. Psychiatric symptoms were significantly reduced in the group assigned to CT, in comparison with TAU, with an estimated between-group effect size of -6.52 (95% CI -10.79 to -2.25, p = 0.003).

Conclusions: CT significantly reduced psychiatric symptoms and appears safe and acceptable in people with schizophrenia spectrum disorders who have chosen not to take antipsychotic medication. A larger, definitive trial is required.

Trial registration: This study is registered as International Standard Randomised Controlled Trial number 29607432.

Key words: Schizophrenia; Cognitive therapy; Psychosis; antipsychotic medication

Declaration of interest: None.

Introduction

Antipsychotic medication is seen as the first line of treatment for schizophrenia and clinical guidelines suggest that there are clear benefits in terms of symptom reduction [1]. In addition, recent studies have also shown that antipsychotic use is associated with decreased mortality overall [2], perhaps because of a protective effect against suicide [2], and have shown significant benefits for relapse prevention [3]. However, there is also evidence that many service users choose to refuse or discontinue their pharmacological treatment. The largest trial [4] to compare atypical antipsychotics found that 74% of patients with a diagnosis of schizophrenia chose to discontinue their medication over 18 months and it is estimated that rates of medication non-compliance in schizophrenia can be as high as 40% to 50% [5]. It is well known that service users with psychosis are often ambivalent about taking medication [6], and recent evidence suggests that the efficacy of such medication has been overestimated while the severity of their adverse effects have been underestimated. A recent systematic review concluded that the improvements claimed for antipsychotics, old and new, are of questionable clinical relevance [7], with most trials failing to demonstrate even minimal improvement using the PANSS, and a recent multiple-treatments meta-analysis [8] found that "although differences in efficacy were seen, they were smaller than those reported for most of the analysed adverse effects" [9]. Recent research suggests that adverse effects include structural abnormalities in brain volume that have previously been attributed to the syndrome of schizophrenia [10], increased risk of sudden cardiac death [11] and substantial weight gain induced by antipsychotics [12], which is associated with cardiovascular and metabolic risks.

Given the cost-benefit profile outlined above, some choices to refuse antipsychotics may reflect a rational decision rather than an irrational consequence of psychosis. It is clear that many people hospitalised with psychosis retain treatment decision-making capacity [13], and a recent review regarding choice and decision making in people using mental health services concluded it is "abundantly clear that service users want to be offered more than just medication" [14]. Cognitive therapy (CT) has been shown to be effective when delivered in combination with antipsychotic medication, with several meta-analyses showing robust support for this approach [15]. Our recent exploratory single-arm trial study evaluated CT for people with psychotic disorders in 20 participants with schizophrenia spectrum disorders who had not been taking antipsychotic medication for at least 6 months [16]; we found significant beneficial effects on primary and secondary outcomes at end-of-treatment and follow-up, good acceptability and no patients significantly deteriorated. However, such a trial clearly suggests the possibility of bias resulting from allegiance effects and non-blind ratings, and the lack of randomisation to a control condition was also problematic; these methodological limitations probably resulted in inflated estimates of treatment effects, since CT for psychosis trials that attempt masking are associated with a reduction of effect sizes of nearly 60% [15].

Therefore, our pilot study aimed to conduct an examination of the feasibility and effectiveness of CT for people with schizophrenia spectrum disorders who had decided not to take antipsychotic medication, under single-blind, randomised controlled conditions. Our primary hypothesis is that CT will be effective in reducing psychiatric symptoms, in comparison to TAU, within this population. We also hypothesised that CT

would reduce dimensions of delusional beliefs and voice hearing, reduce emotional dysfunction and improve real-life functioning and user-defined recovery.

Methods

Trial design: This is a two-site randomized, controlled, single-blind (rater) pilot trial comparing two conditions (CT plus TAU versus TAU control). Our protocol was approved by the National Research Ethics Service of the United Kingdom's National Health Service (NREC: 09/H1014/53).

Participants: Trial entry criteria were that participants were in contact with mental health services, and either met ICD-10 criteria for schizophrenia, schizoaffective disorder or delusional disorder or met entry criteria for an Early Intervention for Psychosis service (operationally defined using PANSS) in order to allow for diagnostic uncertainty in early phases of psychosis and the fact that most early episode cases within the UK will receive their services from such specialist teams, consistent with NICE guidelines. They also either had at least 6 months without antipsychotic medication and experiencing continuing symptoms or never had received antipsychotics and had chosen not to, and all scored at least 4 on PANSS delusions or hallucinations, or at least 5 on suspiciousness/ persecution, conceptual disorganisation or grandiosity. All participants were identified via care coordinators and relevant mental health staff within participating mental health trusts at our 2 sites (Manchester/North West and Newcastle/North East), and were aged 16-65. Exclusion criteria were current receipt of antipsychotic medication; moderate to severe learning disability; organic impairment; lacking capacity to consent to research participation; non-English speaking (since this would prevent the use of standardised assessment instruments); acute inpatient care settings; having received CT for psychosis or, previous CT for other disorders in the last

2 years; and a primary diagnosis of substance or alcohol abuse. Diagnosis was established using case notes and a standardised checklist (ICD-10); all diagnoses were confirmed by a Consultant Psychiatrist (DT), applying the ICD-10 checklist to vignettes based on the PANSS assessments for all cases, including those in early intervention services who did not have a formal diagnosis in their medical records. Diagnoses were as follows: schizophrenia n= 68 (91.9%), Schizoaffective n = 2 (2.7%), Persistent Delusional Disorder n = 3 (4.1%) and Psychosis Not Otherwise Specified n = 1 (1.4%). Further details regarding our ascertainment strategy, referral sources, reasons for choosing not to take antipsychotics and additional participant characteristics are provided elsewhere [17].

Randomisation: Following the baseline assessment, participants were randomised electronically using a 1:1 ratio via OpenCDMS [18]. The randomisation algorithm uses randomised permuted blocks with block sizes of four or six, after first stratifying by site. OpenCDMS then sent out email notification of the allocation to the therapists and trial manager. Thus, the results of the randomisation were concealed from the assessors and randomisation was independent. Participants were randomised to TAU or CT plus TAU. TAU will have been variable and dependent on local service configurations and specific source of referral to the trial; therefore, randomisation was stratified by site in an attempt to control for this variation.

Interventions:

CT plus TAU

In addition to TAU (described below), participants allocated to the therapy arm of the trial received CT based on a specific cognitive model [19]. 26 sessions were offered on an approximately weekly basis for up to a maximum of 9 months, plus up to four

booster sessions in the subsequent nine months. Cognitive therapy requires an individualised, problem-orientated approach and incorporates a process of assessment and formulation, which is manualised. The central features of our approach to treatment of psychosis involves normalising and evaluating the appraisals that people make, helping them test out such appraisals using behavioural experiments and helping them to identify and modify unhelpful cognitive and behavioural responses. A more detailed analysis of the treatment strategies can be found in our treatment manuals [20 21]. Fidelity to the treatment protocol was ensured by regular supervision of the therapists and assessed by rating recordings of sessions using a version of the Cognitive Therapy Scale-Revised [22] (CTS-R) and reviewing written, structured session records that were completed by the therapist after each session. Therapy supervision was provided by means of regular meetings between therapists and the chief investigator. A total of ten sessions were rated on the CTS-R, and all were rated as competent or above.

CT Therapists

In total, 8 therapists contributed to the delivery of CT within the trial. The number of participants treated by each ranged between 2 and 18 (mean = 4.6, SD = 5.5). Sites varied as follows: Manchester/North West (2 therapists), Newcastle/North East (6). 5 were clinical psychologists (doctoral level), 2 were nurses with an additional specialist CT qualification and 1 was a Consultant Psychiatrist with specialist training in CT. All received additional training associated with the trial manual and received regular supervision.

TAU

All participants received treatment as usual plus regular monitoring (incorporating a PANSS assessment from a research assistant), which represents an

enhancement over routine care since it aimed to provide warm, empathic and non-judgemental face-to-face contact, supportive listening, signposting to appropriate local services for unmet needs and crisis management when required (usually by referral to a local crisis team, early intervention service or psychiatric liaison within emergency departments). Treatment as usual was variable across both sites, although both sites were chosen in part because they had comprehensive early intervention services (EIS). In practice, those within EIS (n=43/74: 58.1%) received regular care-coordination and psychosocial interventions including the offer of family interventions, whereas those from other community based services often received little other than irregular contact with care coordinators, and many of these were discharged by these teams within the lifetime of the trial for non-attendance on continued reluctance to accept medication.

Outcomes: Our primary outcome measure was the total score on the *Positive and Negative Syndromes Scale (PANSS: [23],* which is a clinician administered thirty-item semi-structured interview consisting of seven items assessing positive symptomatology (e.g. hallucinations, delusions, conceptual disorganisation), seven items assessing negative symptomatology (e.g. blunted affect, passive/apathetic social avoidance) and sixteen items assessing general psychopathology (e.g. depression, anxiety, lack of insight, guilt). All items are scored between 1 (not present) and 7 (severe). A number of studies have demonstrated the reliability and validity of the PANSS [24]. Inter-rater reliability of the PANSS assessments was assessed regularly (on 9 occasions) over the lifetime of the trial, using both video and role-play assessments with all trial raters (n=5) participating; intra-class correlation coefficients indicated good reliability between raters (mean = 0.83, S.D. = 0.12).

Secondary outcomes included dimensions of psychotic experiences such as severity, distress and disability, measured using the Psychotic Symptom Rating Scales [25], which is a clinician administered semi-structured interview consisting of eleven items assessing dimensions of auditory hallucinations and six items assessing dimensions of delusional beliefs. All items are scored 0 to 4, with higher scores indicating more severe phenomena. Factor analyses show the delusions scale has two subscales (emotional and cognitive) and the hallucinations scale has three subscales (emotional, physical and cognitive) [25]. We also included a user-defined measure of recovery (QPR [26]), which is a questionnaire developed collaboratively with service users, measuring subjective recovery ; we employed a 15 item version that has been shown to be more reliable than the original 22 item version (Cronbach's alpha in our sample was 0.91, showing good internal consistency). Participants rate their agreement with statements on a 5 point Likert scale rating from "strongly disagree" to "strongly agree". Social functioning was assessed using the Personal and Social Performance Scale [27], which is a 100–point single-item rating scale based on an interview that assesses patient's functioning in four areas (socially useful activities, personal and social relationships, self-care and disturbing and aggressive behaviour). We assessed emotional distress using the Beck Depression Inventory for Primary Care (BDI-PC) [28] and the Social Interactions Anxiety Scale (SIAS) [29]. The SIAS has a recommended cut-off of greater than 36, indicating a probable diagnosis of social anxiety disorder[30], and the BDI-PC has a recommended cut-off of greater than 3, indicating a probable diagnosis of major depressive disorder[28]. We recorded prescriptions of antipsychotic and other psychiatric medications. Most assessments occurred in the participants' home. Several other measures were administered (such as EQ5D, the CHOICE, the

Metacognitions Questionnaire and the Personal Beliefs about Experiences Questionnaire), but these were intended for secondary analyses such as predictors of outcome and cost effectiveness; we report on all outcomes that were specified in our published protocol and analysis plan [17].

Post-randomisation, all participants received monitoring assessments every three months up to a total of 18 months. Our variable follow-up period means that participants recruited in the first 18 months of the study (from February 2010 – August 2011) were planned to receive the full 18 month follow-up. Participants recruited thereafter are offered steadily reducing follow-up periods, depending on time of recruitment (this was to maximise value for money, obtaining as much data as possible on those recruited in early phases of the trial, with shorter follow-up periods for those recruited in later phases). The minimum follow-up period is 9 months; the total sample size that could be expected to be available at each follow-up point is shown in Figure 1 i.e. follow-ups at 12, 15 and 18 months inevitably had less participants since those most recently recruited could not be followed up at these time points within the funded resources.

Changes to trial protocol following commencement: Following original ethical approval of the trial in October 2009, several amendments to the protocol were made: the addition of secondary measures including the CHOICE and EQ5D; addition of some secondary measures for an add-on hypothesis about childhood trauma at month 3; removal of some secondary measures at months 3, 6 and 15 in order to reduce participant burden; an ability to retain people if they lose capacity, which was an event that did not actually occur throughout the trial; a minor change to the exclusion criteria

to reflect the population and increase generalisability (allowing inclusion of those with substance dependence as long as it was not the primary diagnosis).

Sample size: Power calculations suggested that, with 30 participants per group, using a t-test with a two-tailed significance level of 0.05, we had over 80% power to detect an effect size of 0.8 (if the significance level were altered to 15%, which may be appropriate for a pilot study, 30 per group provides 80% power to detect an effect size of 0.6). We chose a recruitment target of 80 (40 per site) in order to allow for a dropout rate of up to 25%.

Blinding: Assessors were blind to treatment condition. Many strategies were employed to achieve blind ratings, including: research workers were not involved in the randomisation process; therapists were required to consider room use and diary arrangements in the light of potential blind-breaks; patients were reminded by assessors not to talk about treatment allocation. We had 13 blind breaks reported to our trial manager by research assistants using a standard form, representing 17.6% of participants; therefore, the blind was successfully maintained in 82.4% of participants. Of those where the blind was broken, 4/13 of these were in the TAU condition and 9/13 in the CT condition. In cases where blinding was broken, another rater assessed the patient for all subsequent assessments or the ratings were discussed with a blind rater and consensus reached. This assessment strategy ensured that only a tiny minority of a total of approximately 500 assessments had their validity threatened by lack of rater blinding.

Statistical methods: Analysis was agreed with the data monitoring and ethics committee, and the a-priori analysis plan was published [17]. Analyses were undertaken in Stata (version 12) after completion of endpoint assessments; primary analysis was by

intention-to-treat. Changes in all primary and secondary outcomes were analysed using Stata's xtreg command to fit random effects regression models (essentially, repeated measures ANCOVAs) with summed scores as dependent variables, allowing for attrition and the variable follow-up times introduced by the design of the trial. Covariates included site, gender age and the baseline value of the relevant outcome measure. The use of these models allowed for the analysis of all available data, on the assumption that data were Missing at Random (MAR) [31], conditional upon adjustment for centre, age, gender and observed baseline scores; the MAR assumption seems to be the most realistic, given the planned variation in maximum follow-up times and the many other factors likely to influence drop-out, and is the one routinely used in analyses of longitudinal trial data. We report estimated treatment effects, with their standard errors, significance levels and confidence intervals. For none of the outcomes was there any suggestion that the treatment effects were varying with time of follow-up (there were no significant treatment by time interactions). All treatment effects reported here are estimates of the effects common to all follow-up times.

Role of the funding source: The funders and sponsors of the study had no role in study design, in the collection, analysis, and interpretation of data, in the writing of the report or in the decision to submit the paper for publication.

Results

We finished recruiting for the trial in June 2012 and had a final sample size of 74, with 37 individuals in each trial arm (Manchester n = 41, Newcastle n = 33). We stopped before the target of 80 in accordance with our recruitment timeline, due to limited resources, in order to ensure that we had the possibility to obtain 9 month data

on all participants. The characteristics of the whole sample, and the baseline balance across the 2 groups, are presented in Table 1.

In terms of feasibility of the trial, it is clear from Figure 1 that recruitment was relatively successful: we recruited over target in one of the two sites, and had a final sample of 74 participants (93% of target); our referral:randomised ratio was 2:1; only 3 participants of 143 referrals declined participation after being assessed as eligible (2%), suggesting good willingness to be randomised, and to consider CT, within this population. Those allocated to CT received a mean of 13.3 sessions (s.d.=7.57; range 2 to 26), each session lasting on average 1 hour (this figure does not include the 4 booster sessions that were available). Adherence to CT was reasonably good, with 0/37 (0%) not attending any sessions, and 30/37 (82.1%) receiving at least 6 or more sessions. Retention within the trial was reasonable, with 5/37 withdrawals in each arm, and missing data rates at primary end point and follow-up being just below 30%. This rate of missing data, in addition to recruiting below target, obviously leads to a reduction in statistical power; however, this is not a major concern given that the trial was a pilot study.

(TABLES 1-5 HERE)

(FIGURE 1 HERE)

Table 2 shows the results of the primary outcome (PANSS) and secondary outcomes at each assessment point. Starting with the primary outcome (the PANSS total scores), it can be seen that the average scores are consistently less in the CT group than in the TAU controls. These are reflected in the estimates of the treatment effects provided in Table 3, with an estimated between-group effect size (unstandardised) for the PANSS total score of -6.52 (95% CI -10.79 to -2.25, p = 0.003), which equates to a

standardised effect size (Cohen's d) of 0.46 (lower PANSS scores are preferable). The effects on the positive and general subscales are consistent with this finding, but there seems to be little or no effect of CT on negative symptoms. Visual inspection of the PANSS data makes it clear that, on average, there was not an overall deterioration in either group.

Looking at the secondary outcomes, the estimated treatment effects for the PSYRATS scores in Table 3 are consistent with the findings for the primary outcome, but not all are statistically-significant. For the other outcomes, we found a significant effect in favour of CT for social functioning (PSP), but no differences on our measures of recovery (QPR), depression (BDI) or anxiety (SIAS).

We also report numbers of participants in each group (completer-only data i.e. observed cases) achieving a 25%, 50%, 75% and 100% improvement/deterioration on adjusted PANSS total scores [32] at both 9 months and 18 months (Table 4), as has been recommended for trials using the PANSS[33]. Examining the proportion of participants achieving good clinical outcomes in each condition (defined using an improvement of >50% in adjusted PANSS total scores), we found that, at 9 months 7/22 from CT (31.8%) and 3/23 from TAU (13.0%) had achieved good clinical outcomes, and at 18 months 7/17 from CT (41.2%) and 3/17 from TAU (17.6%) had achieved good clinical outcomes. We also examined significant deteriorations (defined using a deterioration of >50% in adjusted PANSS total scores); there were 2 such participants in each condition. We also examined serious adverse events (SAEs) as defined by the Ethics Committee; there were 8 in total, with 2 such events in CT (both of which occurred post therapy; one attempted overdose, one presenting risk to others) and 6 such events in TAU (two deaths, both of which were deemed unrelated to trial participation/mental health; three

compulsory admissions to hospital for treatment under the mental health act and one attempted overdose). We also examined voluntary hospital admissions during the treatment phase; the data regarding type, number and length of stay for hospital admissions is provided in table 5. There was only one admission in the follow-up phase, which was voluntary and lasted 4 days (this was in the CT arm). All SAEs and hospital admissions were in separate participants.

We also examined the use of antipsychotic medication throughout the lifetime of the trial: 10/37 participants in CT were prescribed antipsychotics post-randomisation (8 during the treatment window, 2 during the follow-up phase) versus 10/37 in TAU (9 during the treatment window, 1 during the follow-up phase). In order to explore the potential contribution that medication may have contributed to individual participants, the extent of change in PANSS scores for those who commenced antipsychotics by 9 and 18 months are also shown in Table 4 (the numbers who had initiated antipsychotics within each category being indicated with the superscript values). Of those in CT prescribed antipsychotics in the treatment phase, 1 was also prescribed antidepressants, and of those in TAU prescribed antipsychotics in the treatment phase 5 were also prescribed antidepressants. In addition to this, there were 9 participants in CT arm taking antidepressants in the treatment phase (with no new cases in follow-up) and in TAU we had 8 participants taking antidepressants in the treatment phase (with 2 new cases in follow-up).

Discussion

To our knowledge, this is the first RCT of CT for people with schizophrenia spectrum disorders who have chosen not to take antipsychotic medication. Our trial has shown that CT for this population does significantly reduce the severity of psychiatric

symptoms in this population. As well as psychiatric symptoms, CT significantly improved personal and social functioning and certain dimensions of delusional beliefs (cognitive) and voice-hearing (cognitive and physical). It did not significantly affect the amount of distress associated with delusional beliefs or voice-hearing, or levels of depression, social anxiety and self-rated recovery. A large definitive trial with a wider range of outcomes would answer such speculation.

On average, neither group deteriorated over time, in a population that have been assumed to deteriorate without total adherence to medication [34]; in fact, some participants in the treatment as usual condition who were not taking medication achieved good clinical outcomes, and more did with the addition of CT. However, it is also clear that some individual patients who were not taking medication did experience deterioration and adverse events, and that this was the case in both arms (it is also possible that we missed some such events, given high rates of missing data and non-engagement with services). We also demonstrated that CT is an acceptable intervention for a population who are usually seen as very challenging to engage by mental health services, with relatively low drop-out/withdrawal rates and only 3 of 143 referrals refusing randomisation after assessment as eligible.

These results are consistent with findings from clinical trials of CT for psychosis to date; most trials have found that severity of psychiatric symptoms can be reduced over a moderate timeframe in people who are taking antipsychotic medications, with an average effect size of 0.4 [15]. Our study found a similar effect size in people who had chosen not to take such medication (ES=0.46). Although this is a small-to-moderate effect size, it is interesting to note that the effect size on psychiatric symptoms observed in our study is similar to the median effect size reported for overall symptoms in a

recent large meta-analysis of 15 antipsychotic medications versus placebo (k=212; n=43049; ES=0.44) [8]. The baseline PANSS total scores of our trial are notably higher than most CT for psychosis trials, suggesting that our results may be reasonably generalisable and are not attributable to participants being relatively well at study entry (our sample would be correspond to a "moderately ill" population according to thresholds for the PANSS[35]); indeed, many of the participants were viewed as challenging to engage by their clinical teams, with some being discharged as a result, and our therapists frequently had to work hard to engage them and identify a shared goal. CT appeared to be acceptable to this population, with zero participants attending no sessions and only 7/37 attending less than 6. Given that equal numbers in each arm commenced medication, it seems unlikely that the effects observed are due to medication, especially since more commenced antipsychotics during the initial treatment window in the TAU condition. Examination of the improvement or deterioration experienced by those who commenced medication (in Table 4) also suggests that the benefits observed are not attributable to antipsychotics.

Our trial demonstrates methodological rigour in several ways. Importantly, we pre-specified the primary and secondary outcomes to be analysed, reducing the likelihood of type 1 errors. The use of more than one should increase generalisability to routine clinical service provision. However, there are some methodological difficulties with our trial. We did not measure treatment exposure prior to study entry (except for recent antipsychotic medication and CT), so are unable to allow for this in our analyses. We did not correct for multiple comparisons (for example, using Bonferroni's correction); however, we only had one primary outcome, and given that this is a pilot study, it would seem overly conservative to apply a more stringent alpha for secondary

outcomes. It is possible that the use of acceptance into an early intervention service as an alternative to diagnosis as inclusion criteria may limit generalisability of our findings to settings that do not have such specialist teams. Similarly, the fact that we excluded people who were in inpatient settings also limits generalisability to those with acute episodes requiring admission to hospital, and those who are referred to a clinical trial may not be representative of all who refuse medication (although we had very few referred who refused to participate). Our trial is also unlikely to be generalisable to service users who are presenting significant risk to themselves or the community, as they would be likely to be managed using community treatment orders that require medication compliance. The lack of a control group that included non-specific factors such as contact time, warmth and empathy, also means that we are unable to exclude the possibility that the observed effects are due to such non-specific factors. Perhaps most importantly, our trial had low statistical power with a small sample size and a relatively high attrition rate (approaching 30% at our primary end points). Given the trend observed in trials of specific psychological therapies such as CT for psychosis, which have shown that effect sizes are reduced when indices of study quality (such as adequate statistical power and active comparators) are controlled for [15], it is likely that our effect sizes are inflated. Therefore, an adequately powered definitive randomised controlled trial is required. A larger definitive trial would allow for analysis of factors such as therapist effects and subgroups (e.g. participants not taking any medications).

There are several clinical implications arising from this study, although they need to be considered cautiously, given the limitations of a pilot study. Given that the largest factor in our participants choices not to take antipsychotics was side effects [17], it is important to be able to have alternative evidence-based treatments for people who

choose not to take antipsychotics. Given that we found CT reduced severity of psychiatric symptoms and increased social functioning in people with schizophrenia spectrum disorders without the use of antipsychotic medication, such an approach may provide the benefits of symptom-based improvement without the associated risks of serious side effects. Thus, it may be possible to offer informed choices to service users who retain decision making-capacity if there is no risk to self or others (a comprehensive risk assessment would be required to inform this). We are not advocating that people who derive benefit from antipsychotic medication should consider discontinuation; rather, we are advocating for evidence-based alternatives for those who choose not to on the basis of side effects or inefficacy (it is important to consider that this may be as high as half of all service users with schizophrenia spectrum disorders[5]). A collaborative approach to decision making may also result in a better response for those who choose to take antipsychotics, since the quality of relationship with the prescribing clinician is associated with attitudes to and adherence with medication [36]; in this context, it is also worth noting that 20 of our participants started antipsychotic medication at some point after having originally chosen not to. Consistent with this approach, the recently published NICE guidelines for psychosis and schizophrenia in children and young people recommend that service users and carers should be entitled to choose psychosocial interventions, such as CT, in the absence of antipsychotics [37].

Research in Context:

Systematic Review: Recent systematic reviews and meta-analyses [1 15 37] have found that, while there is robust evidence that CT for psychosis in addition to antipsychotics is

superior to treatment as usual, there are no randomised controlled trials of CT in people with psychotic disorders who are not taking antipsychotics.

Interpretations: Our study suggests that CT is an acceptable, safe and effective treatment for people who choose not to take antipsychotics, although a larger definitive trial is required, given that this is a pilot trial.

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Contributors: All authors were involved in the design of the study and the ongoing management and delivery of the trial, and contributed to drafts of this manuscript. AM, the chief investigator, conceived of the study, prepared the protocol, contributed to the training and supervision of the therapists and supervision of the researchers, had overall responsibility for the day to day running of the study, interpreted the data, and took the lead on writing this report. He is the guarantor for the study. AM, DT, PH, AB, RD, NC, TC, PC, TG and VL participated in preparation of the treatment protocol and the training and supervision of the therapists. DT and AB managed the additional site. AM,

MP, HS and DT trained the researchers in the psychiatric interviews, supervised and monitored standards of psychiatric interviewing and assessment throughout the trial. DT also advised on diagnostic ratings and exclusions. MP was the trial manager. She supervised and coordinated recruitment, contributed to training of research staff, and was responsible for staff management and overall coordination of the study. HS, LD, AC, KI and ST were responsible for maintaining reliability of assessment procedures and data collection. GD was the trial statistician. He advised on randomisation and all statistical aspects of the trial, developed the analysis plan, and performed the statistical analyses and is guarantor in this respect. LD was the trial health economist. RB was a service user consultant involved in all aspects of the study.

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Figure 1: CONSORT Diagram for entry to study

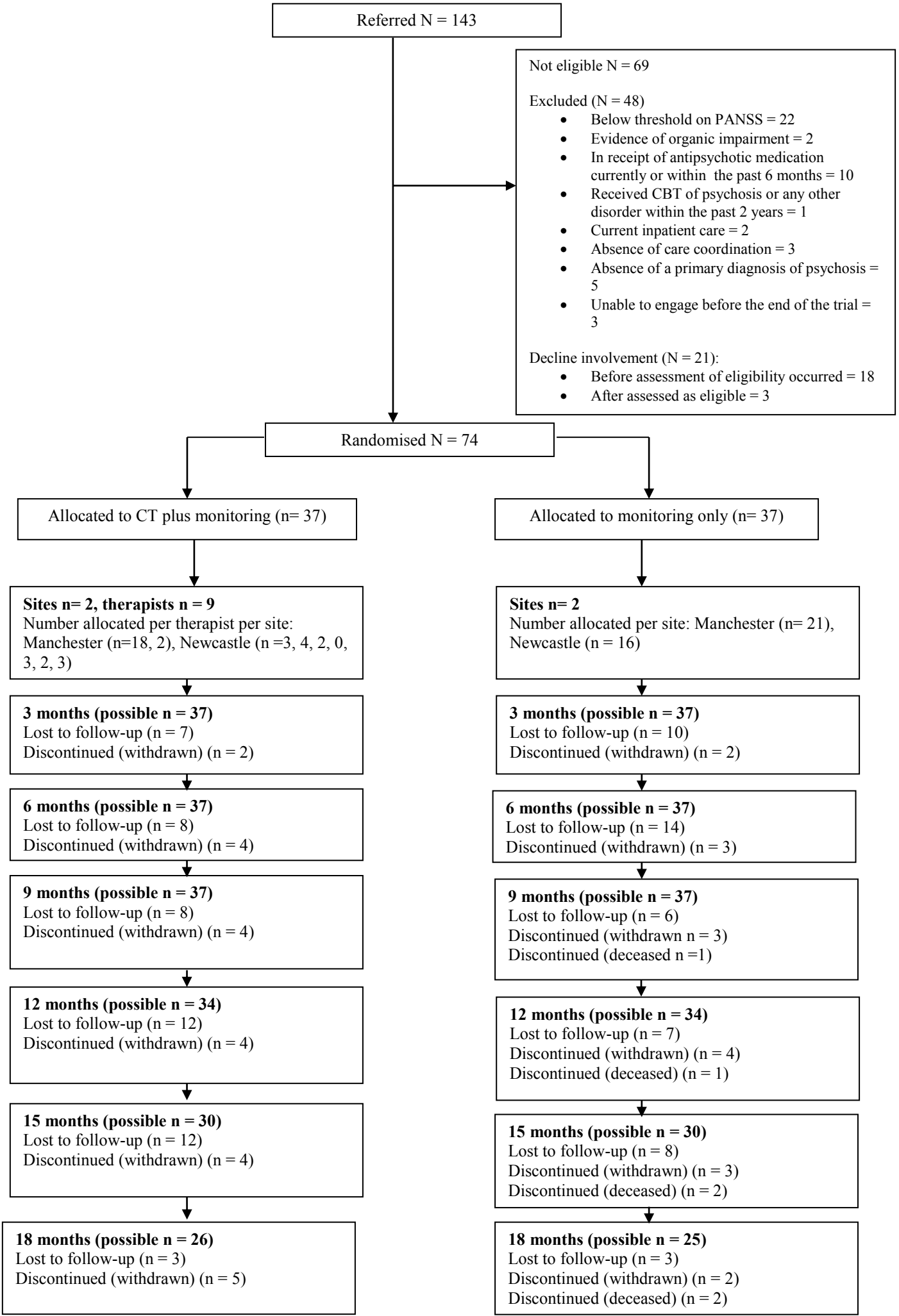
Referred N = 143
Not eligible N = 69
Excluded (N = 48)
Below threshold on PANSS = 22
Evidence of organic impairment = 2
In receipt of antipsychotic medication currently or within the past 6 months = 10
Received CBT of psychosis or any other disorder within the past 2 years = 1
Current inpatient care = 2
Absence of care coordination = 3
Absence of a primary diagnosis of psychosis = 5
Unable to engage before the end of the trial = 3
Decline involvement (N = 21):
Before assessment of eligibility occurred = 18
After assessed as eligible = 3
Randomised N = 74
Allocated to CT plus monitoring (n= 37)
Allocated to monitoring only (n= 37)
Sites n= 2, therapists n = 9
Number allocated per therapist per site: Manchester (n=18, 2), Newcastle (n =3, 4, 2, 0, 3, 2, 3)
Sites n= 2
Number allocated per site: Manchester (n= 21), Newcastle (n = 16)
3 months (possible n = 37)
Lost to follow-up (n = 7)
Discontinued (withdrawn) (n = 2)
3 months (possible n = 37)
Lost to follow-up (n = 10)
Discontinued (withdrawn) (n = 2)
6 months (possible n = 37)
Lost to follow-up (n = 8)
Discontinued (withdrawn) (n = 4)
6 months (possible n = 37)
Lost to follow-up (n = 14)
Discontinued (withdrawn) (n = 3)
9 months (possible n = 37)
Lost to follow-up (n = 8)
Discontinued (withdrawn) (n = 4)
9 months (possible n = 37)
Lost to follow-up (n = 6)
Discontinued (withdrawn n = 3)
Discontinued (deceased n =1)
12 months (possible n = 34)
Lost to follow-up (n = 12)
Discontinued (withdrawn) (n = 4)
12 months (possible n = 34)
Lost to follow-up (n = 7)
Discontinued (withdrawn) (n = 4)
Discontinued (deceased) (n = 1)
15 months (possible n = 30)
Lost to follow-up (n = 12)
Discontinued (withdrawn) (n = 4)
15 months (possible n = 30)
Lost to follow-up (n = 8)
Discontinued (withdrawn) (n = 3)
Discontinued (deceased) (n = 2)
18 months (possible n = 26)
Lost to follow-up (n = 3)
Discontinued (withdrawn) (n = 5)
18 months (possible n = 25)
Lost to follow-up (n = 3)
Discontinued (withdrawn) (n = 2)
Discontinued (deceased) (n = 2)

Table 1: Baseline characteristics: Means and SDs for variables for total sample and for each group

	Whole sample (N=74)	CT plus TAU (N=37)	TAU only (N=37)
Age	31.47 (12.27)	32.95 (13.11)	29.68 (11.95)
Male: Female ratio (n)	39:35	17:20	22:15
PANSS Total	71.55 (13.76)	70.24 (13.75)	73.27 (13.42)
PANSS Positive	20.89 (4.91)	20.30 (5.22)	21.65 (4.47)
PANSS Negative	14.31 (4.61)	13.54 (3.17)	15.49 (5.26)
PANSS General	36.18 (7.70)	36.41 (7.94)	36.14 (7.05)
PSYRATS Unusual Beliefs - Cognitive	10.27 (3.59)	10.11 (4.18)	10.43 (2.91)
PSYRATS – Unusual Beliefs - Emotional	5.08 (2.58)	5.17 (2.69)	5.00 (2.51)
PSYRATS Voices - Cognitive	6.52 (5.29)	5.28 (5.13)	7.73 (5.23)
PSYRATS Voices - Emotional	6.90 (6.23)	5.86 (6.43)	7.92 (5.93)
PSYRATS Voices - Physical	6.47 (5.29)	5.62 (5.40)	7.37 (5.10)
PSP	53.43 (16.57)	56.84 (16.45)	50.03 (16.19)
QPR Intrapersonal	33.61 (12.42)	34.19 (12.17)	32.97 (12.85)
QPR Interpersonal	12.76 (2.82)	13.05 (2.77)	12.44 (2.88)
BDI-PC total	10.011 (4.68)	10.54 (5.21)	9.41 (4.03)
SIAS total	40.77 (18.03)	40.43 (19.76)	45.15 (15.19)
PANSS G12 (Insight)	3.12 (1.66)	3.03 (1.67)	3.20 (1.67)
PANSS Insight > 3: moderate or higher problems (n)	34	17	17

Variable	3 CT N=37	months TAU N=37	6 CT N=37	months TAU N=37	9 CT N=37	months TAU N=37	12 CT N=34	months TAU N=34	15 CT N=30	months TAU N=30	18 CT N=26	months TAU N=25
PANSS total	62.93 (13.72) N=28	72.88 (15.56) N=24	59.96 (14.47) N=23	66.95 (11.70) N=19	57.95 (14.99) N=22	63.26 (13.21) N=23	58.56 (18.85) N=18	68.33 (15.03) N=21	54.68 (14.61) N=19	69.94 (14.35) N=16	56.47 (18.22) N=17	71.24 (20.35) N=17
PANSS positive	18.14 (5.34) N=28	21.71 (5.83) N=24	17.04 (5.36) N=23	18.32 (4.40) N=19	16.00 (5.94) N=22	17.00 (4.85) N=23	16.32 (7.94) N=19	18.62 (5.26) N=21	14.05 (5.36) N=19	19.44 (5.75) N=16	14.63 (6.18) N=19	18.83 (7.26) N=18
PANSS negative	13.00 (3.16) N=28	14.88 (5.77) N=24	12.48 (3.63) N=23	13.95 (3.76) N=19	12.5 (3.38) N=22	14.26 (4.21) N=23	12.61 (4.24) N=18	15.95 (5.89) N=21	12.05 (3.85) N=19	16.19 (5.49) N=16	12.53 (2.83) N=17	16.59 (6.65) N=17
PANSS general	31.79 (7.89) N=28	36.29 (8.26) N=24	30.43 (8.63) N=23	34.68 (7.17) N=19	29.45 (7.68) N=22	32.00 (6.98) N=23	29.78 (7.95) N=18	33.76 (7.80) N=21	28.58 (7.71) N=19	34.31 (7.10) N=16	29.22 (10.51) N=18	35.82 (9.74) N=17
QPR Intrapersonal	38.83 (12.06) N=24	33.26 (14.03) N=23	36.10 (16.77) N=21	34.74 (11.62) N=19	38.41 (14.48) N=27	36.88 (9.17) N=24	40.06 (16.88) N=18	35.50 (10.10) N=18	44.06 (16.24) N=18	31.43 (13.37) N=14	42.41 (19.60) N=17	33.94 (9.57) N=16
QPR Interpersonal	12.13 (2.66) N=24	12.57 (3.58) N=23	13.00 (3.88) N=22	12.05 (4.89) N=21	12.96 (3.84) N=27	11.71 (2.69) N=24	14.11 (3.50) N=18	13.11 (2.52) N=18	13.11 (4.91) N=18	11.29 (4.07) N=14	13.77 (4.75) N=17	12.31 (1.85) N=16
PSP	59.81 (16.55) N=27	49.70 (14.46) N=24	59.74 (17.88) N=23	51.89 (16.09) N=19	65.00 (12.75) N=23	56.74 (15.02) N=23	65.37 (17.63) N=1	52.95 (15.50) N=21	65.84 (18.22) N=19	53.53 (18.75) N=15	64.74 (20.24) N=19	55.94 (20.29) N=18
BDI	7.83 (5.58) N=24	9.65 (4.69) N=23	7.57 (5.89) N=21	7.37 (3.61) N=19	6.35 (5.93) N=26	7.14 (3.35) N=21	7.44 (6.34) N=18	7.00 (3.54) N=17	4.50 (4.05) N=16	7.38 (4.29) N=13	5.50 (5.63) N=16	7.38 (5.16) N=16
SIAS	35.18 (18.75) N=22	44.53 (13.21) N=19	37.63 (18.40) N=19	40.78 (12.88) N=18	31.71 (16.34) N=24	40.48 (13.88) N=21	30.00 (22.38) N=15	41.86 (14.87) N=14	28.59 (18.21) N=17	45.27 (16.44) N=11	31.31 (20.87) N=16	44.06 (18.21) N=16

PSYRATS Delusions - Cognitive	7.82 (4.97) N=27	9.57 (3.75) N=23	7.78 (4.88) N=23	8.00 (3.41) N=18	6.63 (5.32) N=24	7.28 (4.99) N=25	6.00 (5.75) N=19	8.63 (4.21) N=19	3.47 (4.66) N=19	8.81 (4.36) N=16	5.32 (5.39) N=19	7.18 (4.76) N=17
PSYRATS Delusions - Emotional	3.85 (3.21) N=27	4.78 (2.88) N=23	3.61 (3.24) N=23	3.28 (3.14) N=18	3.21 (3.36) N=24	2.92 (2.75) N=25	3.05 (3.37) N=19	4.11 (2.94) N=19	1.26 (2.51) N=19	3.38 (2.68) N=16	2.21 (2.72) N=19	3.47 (2.63) N=17
PSYRATS Voices – Cognitive	3.52 (4.78) N=27	6.78 (5.78) N=23	2.26 (3.89) N=23	6.00 (5.45) N=19	2.73 (4.46) N=26	4.82 (5.29) N=27	3.25 (3.70) N=20	5.37 (5.92) N=19	2.42 (3.88) N=19	5.94 (5.13) N=17	0.79 (2.37) N=19	5.65 (5.36) N=17
PSYRATS Voices – Emotional	3.41 (5.40) N=27	5.96 (6.09) N=23	2.35 (4.25) N=23	4.26 (5.95) N=19	2.81 (5.02) N=26	5.07 (5.90) N=27	3.74 (5.53) N=19	4.26 (6.04) N=19	2.00 (3.84) N=19	5.12 (6.12) N=17	0.50 (2.12) N=18	6.00 (6.49) N=18
PSYRATS Voices - Physical	4.37 (5.49) N=27	7.04 (5.92) N=23	3.00 (4.84) N=23	5.37 (5.20) N=19	3.31 (4.76) N=26	4.82 (5.41) N=27	4.35 (4.67) N=20	5.76 (5.93) N=21	2.58 (4.02) N=19	5.94 (4.89) N=17	1.11 (3.32) N=19	6.83 (6.21) N=18

Table 2: Means, SDs and N for primary and secondary outcome variables at 3-, 6-, 9-, 12-, 15- and 18 months

Table 3 Treatment effect estimates (common to all follow-up times)

Primary Outcome	Estimate*	s.e.	p-value	95% confidence interval
PANSS total	-6.52	2.18	0.003	-10.79 to -2.25
PANSS positive	-2.22	0.91	0.015	-4.00 to -0.44
PANSS negative	-1.02	0.67	0.130	-2.35 to +0.30
PANSS general	-3.63	1.21	0.003	-5.99 to -1.27
Secondary Outcomes				
PSYRATS unusual beliefs cognitive	-2.08	0.82	0.011	-3.69 to -0.47
PYSRATS unusual beliefs emotion	-0.70	0.51	0.170	-1.71 to +0.30
PSYRATS voices cognitive	-2.10	0.95	0.028	-3.96 to -0.23
PSYRATS voices emotion	-1.44	1.06	0.174	-3.52 to +0.64
PSYRATS voices physical	-1.76	0.89	0.048	-3.51 to -0.02
QPR *	+3.32	1.90	0.080	-0.39 to +7.04
PSP*	+5.47	2.70	0.043	+0.18 to +10.77
BDI	-0.73	0.79	0.357	-2.29 to +0.83
SIAS	-1.63	3.17	0.607	-7.84 to +4.58

* Negative estimates indicate that, on average, scores for the CT group were lower than in TAU, except on these items, where a higher score is preferable.

Table 4: Number of participants achieving improvement/deterioration on adjusted PANSS total scores at 9 and 18 months

		Increase (deterioration)						Reduction (improvement)			
	Total N	100%+	75-100%	50-74%	25-49%	0-24%	0% change	0-24%	25-49%	50-74%	75-100%
CT (9m)	22	1[(1)]	0	0	1[(1)]	3	2[(1)]	3[(1)]	5[(2)]	4	3[(2)]
TAU (9m)	23	0	0	0	2	2[(1)]	2[(1)]	9[(3)]	5[(2)]	2	1
CT (18m)	17	0	0	1	1	0	0	4[(2)]	4	6[(2)]	1
TAU (18m)	17	0	0	2	2[(2)]	3[(1)]	1	4[(2)]	2	2[(1)]	1

NOTE: superscript numbers [(n)] indicate the number of participants who had commenced antipsychotic medication, of the total number N within each change category.

Table 5 Hospital admissions during the treatment phase

	CT plus TAU		TAU	
	N participants admitted	**Mean no. days in hospital (SD)**	**N participants admitted**	**Mean no. days in hospital (SD)**
Voluntary admission	4	12.25 (9.54)	1	27.00 (0.00)
Compulsory admission	0	0.00 (0.00)	3	42.00 (22.65)